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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,222	THOMAS ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-24,32 and 43-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24,32 and 43-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/31/05 has been entered.

Applicants' Amendments and Remarks, filed 5/31/05, have been entered. Claims 20, 43, 49 are amended; claims 20-24, 32, and 43-57 are pending and under current examination.

Response to Arguments

The prior rejection of claims 43-57, under 112, 1st paragraph, is withdrawn in view of Applicants' arguments and/or amendments to the claims. Applicants' arguments are found to be persuasive with regard to the type of promoter used in the claimed invention, namely that the amendment to the claims reciting a spatially or temporally restricted promoter. The claimed invention is found to be enabled with regard to the types of genes and nucleic acids that are to be deleted by the claimed method.

The prior rejection of claims 20-24 and 32 under 112, 2nd paragraph, is withdrawn in view of Applicants' amendment to the claims now reciting "A DNA molecule."

The prior rejection of claims 20-24, 32 and 43-45, as being anticipated by Russ *et al.* under 102(b) is withdrawn. The claims, as amended, are no longer anticipated by Russ because Russ do not teach a spatially or temporally restricted promoter, as they teach the pgk (mouse phosphoglycertae kinase) promoter and the simian virus 40 promoter. Neither of these promoters are spatially or temporally restricted. It is noted that Applicants argue that Russ *et al.*'s method, "[R]esult in transient expression with no spatial or temporal restriction. To use a promoter with activity restricted in time or by tissue would not achieve the goal of the Russ *et al.* method, which is to remove all viral sequences throughout the treated organism." See pp. 11-12, bridging ¶. In response, the Examiner notes that there is no recitation of transient expression in Russ *et al.*, because the vectors in this piece of art are directed to integrating retroviral vectors. Thus, this is not considered transient.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-24, 32, 43-45, 49-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dymecki [**U.S. Pat. No.** 6,774,279 B2, published August 10, 2004, filed May 30, 1997] when taken with Von Melchner *et al.* [WO 97/07223, Published 27 February 1997] in further view of Abuin *et al.* [**Mol. And Cell. Bio.**, 16(4):1851-1856 (April 1996)].

The claims are directed to a DNA molecule for removing a nucleic acid sequence that has been inserted into a host cell, the DNA molecule comprising, flanked by recombinase sites, a) a spatially or temporally restricted promoter operably linked to a b) recombinase gene, c) said nucleic acid sequence to be removed. In further embodiments, the claims are directed to methods for deleting a nucleic acid sequence from a mouse cell genome in a regulatable manner using said

nucleic acid sequence, and a transgenic mouse comprising said DNA sequence. In specific embodiments, the recombinase site can be loxP or FRT and the recombinase gene can be Cre or FLP; the nucleic acid sequence is a wild-type allele or fragment thereof of a gene.

Dymecki teach methods of site-specific recombination of DNA into the genome of a mammal. See Abstract. Particularly, they teach methods utilizing either Flp or Cre recombinases to introduce specific deletions into the mouse genome. They teach that a two recombinase system would allow for efficient use of the first recombinase to generate a mutation, and the second recombinase to remove selectable markers, which can confound interpretation of study. See col. 2, lines 1-15. They teach methods of *in vivo* genetic engineering utilizing Flp (or Cre) recombinase activity to catalyze site-specific recombination in cells, which can include germ line cells or somatic cells. See col. 2, lines 53-65. Further, that this system can be used in various methods, such as in activation of ectopic expression of a gene during development, inactivation of a gene at a specific time, or in a specific tissue, or identifying a cell lineage by activation or inactivation of a gene. The gene that is studied using this method can be varied, for example, a developmental gene, an essential gene, or a selectable marker. See col. 4, lines 1-10. They teach that the non-human mammal can have this genetic material stably or excisably integrated into its genome, and that it can be transmitted through the germ line to succeeding generations. They teach that the mammal can include mice, and that the

introduction of the transgene can be made by various methods known in the art. See col. 4, lines 23-57. They teach that that a controlled recombinase target site can be used to engineer tissue-specific mutations, or to assess the effect of ectopic expression in a subset of cells, within an otherwise normal organism, and that this method is particularly useful in cases of studying the effect of lethal or otherwise deleterious mutations, or where the null mutations of a gene do not result in an observable phenotype. See col. 6-7, bridging ¶. They teach that the particular transgene can have the recombinase operably linked to a regulatory region, wherein this regulatory region can be a promoter, enhancer, etc. These regulatory regions can be regulated by, for example, developmental stage, or particular factors. See col. 8, lines 29-67. Dymecki teach that Cre/*loxP* can be used to control a series of recombination events by expression the Flp and Cre recombnases independently of each other; particularly, wherein the second transgene encodes a marker, for example, to trace cell lineages. See col. 10-11, bridging paragraph.

Dymecki do not teach that the transgene is a single transgene wherein the transgene is flanked by recombinase sites. However, prior to the time of the claimed invention, Von Melchner *et al.* teach self-deleting vectors for gene therapy. In particular, they teach utilizing retroviruses in to introduce genes into mammalian genomes. See p. 2, 2nd full paragraph. In particular, they teach that retroviral vectors are the most efficient means to transduce foreign genes into mammalian cells (page 3, 1st full ¶) and that such a vector would contain site-

specific recombinases, such as Cre and loxP, or Flp and frt. Particularly, they teach that the site-specific recombinase can be within one vector (or encoded in a separate vector). See p. 4. They teach that these vectors can then be deleted after introduction into the mammalian cell genome, for example, to remove proviral genome sequences (see p. 5, 3rd paragraph). In particular, they teach a vector that is flanked by recombinase sites (loxP), has a promoter operably linked to a recombinase gene, and a nucleic acid of interest to be deleted. See Figure 9-A.

Accordingly, in view of Dymecki and Von Melchner *et al.*, it would have been obvious for one of skill in the art to modify the techniques to produce transgenic non-human mammals, as taught by Dymecki, using a vector as taught by Von Melchner *et al.*, in order to excise a gene of interest (such as a marker gene), with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification, as Dymecki contemplate removal of selectable markers, because they may interfere with the study of the resultant animal, and Von Melchner teach that their vectors can be used to introduce site-specific mutations into the mammalian genome. Abuin *et al.* provide further motivation, as they teach that it is an art-recognized goal to excise selection markers when producing transgenic mice. For example, they state that one would want to remove selectable markers in order to increase the manipulations that can be done, or for analysis. See Abstract. Furthermore, they teach that, "[T]he exogenous promoter and enhancer elements required for the expression of these

selectable markers have the potential to interfere with endogenous regulatory elements present in the vicinity of the targeted mutation. Therefore, it may be sometimes advantageous to remove selectable markers after gene targeting." See p. 1851, 2nd column, 1st paragraph. Abuin *et al.* further contemplate utilizing the Cre/*loxP* system in order to excise these exogenous markers (see p. 1851, 2nd paragraph). They teach that the excision of markers provide several advantages in the production of transgenic animals by allowing for additional targeting events at different loci and allows for the use of selection-based assays to study the cellular roles and functional interactions between genes, it would alleviate any interference of expression, and to allow for an unlimited number of targeting events in mammalian cell lines which can be used in subsequent genetic analysis. Furthermore, by excision of a selectable marker, could provide for a system to assay genes whose functions are assayed at the cellular level. See p. 1855, 2nd column, last paragraph.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 46-48 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dymecki [**U.S. Pat. No.** 6,774,279 B2, published August 10, 2004, filed May 30, 1997] when taken with Von Melchner *et al.* [WO 97/07223, Published 27 February 1997] in further view of Abuin *et al.* [**Mol. And Cell. Bio.**, 16(4):1851-

1856 (April 1996)], as applied to claims 20-24, 32, 43-45, 49-56 above, and further in view of Vidal *et al.* [**Mol. Reprod. And Dev.**, 51:274-280 (1998)], and the promoter is specific to male or female gametic tissue.

Dymecki, Von Melchner and Abuin are described above. Although Dymecki contemplate utilizing promoters which can be used in order to express a transgene during a specific developmental stage or tissue, they do not specifically teach utilizing a male or female gamete-specific promoter. However, prior to the time of the claimed invention, Vidal teach the generation of transgenic mice using a testicular Cre recombinase driven by promoter sequences derived from synaptonemal complex protein 1 (*Sycp1*), which is expressed in an early stage of male meiosis. They teach utilizing two transgenes, one with the *Sycp1-Cre* transgene, and one wherein the *LoxP* sites flank the βgeo coding region, the *Pgk1* promoter, or the *tk-neo* cassette inserted into the Rxrα locus. See Abstract, and Methods & Materials. In particular, Vidal teach that using Cre/*LoxP*, one can introduce predetermined mutations into the mouse genome, however, many of these mutations can result in early lethal phenotypes. Thus, by the use of temporal and spatial control of recombinase (utilizing tissue-specific or induce promoters), one could overcome these limitations. Vidal specifically teach that Cre expression can be used to target testicular germ cells to generate mutations at predetermined loci during meiosis, to define the role, in spermatogenesis, of any gene of interest. See p. 274, col. 1-2, bridging paragraph.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art to modify the vector, as taught by Dymecki, Von Melchner and Abuin, to utilize a gamete-specific promoter, such as *Sycp1*, as taught by Vidal *et al.*, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification, as Dymecki clearly teach using tissue or developmentally-specific promoters, and Vidal *et al.* teach that utilizing a gamete-specific promoter, such as *Sycp1*, would be useful in studying gene function during spermatogenesis.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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